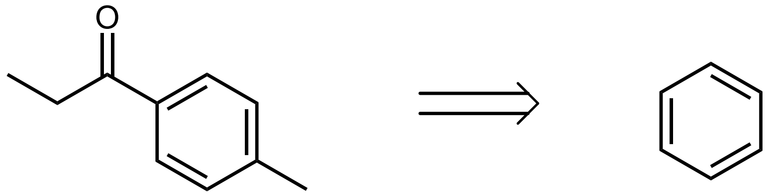
Retrosynthesis of Benzene Derivatives

This Core Concept Sheet covers retrosynthetic analysis of benzene derivatives. Herein, the order of reactions used is crucial to consider, primarily due to the directing effects of ring substituents.

For a more thorough overview of directing effects, see the Aromaticity Core Concept Sheet and accompanying Aromaticity worksheet.

Worked Example 1



target product **starting material**

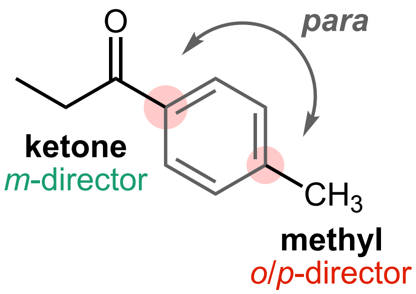
To begin, lets consider a series of guiding questions:

A. What **new functional groups** are present?

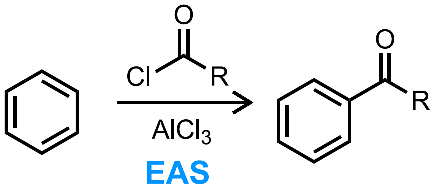
B. What is the **relationship** of the new groups (*ortho, meta,* or *para*)?

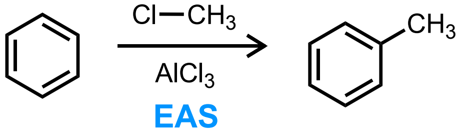
C. What are the **directing effects** of the new groups (*o*/*p*-director or *m*-director)?

If we consider these questions, we see that (A) we have a **ketone** and a **methyl** group;. (B) the ketone and methyl group are **para** to each other; and (C) the **ketone is a *m*-director** whereas the **methyl group is an *o*/*p*-director**.



D. **What types of reactions** (e.g. EAS, NAS, benzylic reactions, oxidation, reduction) could introduce a ketone and a methyl group in a para relationship?

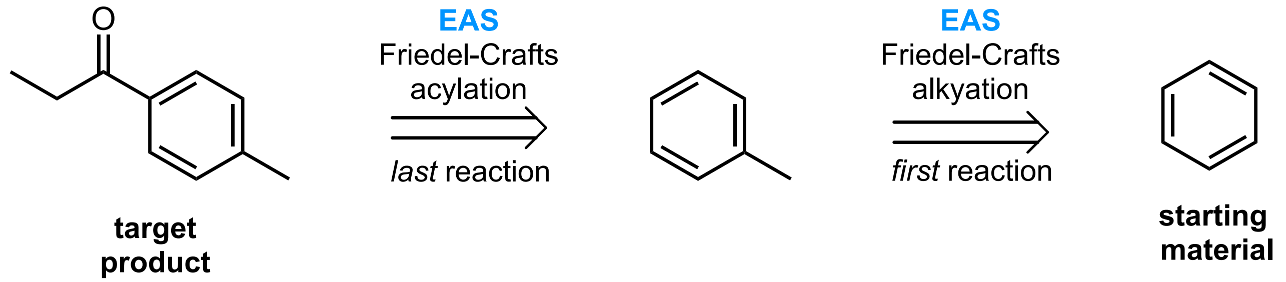




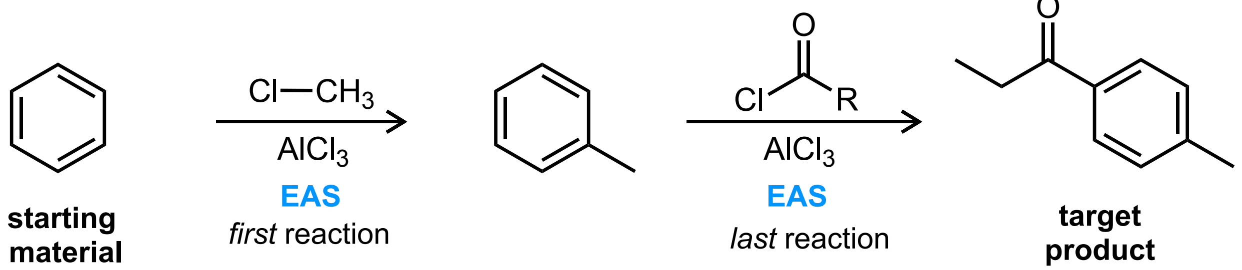
E. Finally, what order of these reactions is needed to achieve the para relationship?

Since the methyl group (or any alkyl group) would direct the next EAS reaction to the *para* site, we can conclude that **we need to do the EAS alkylation first, then the EAS acylation.**

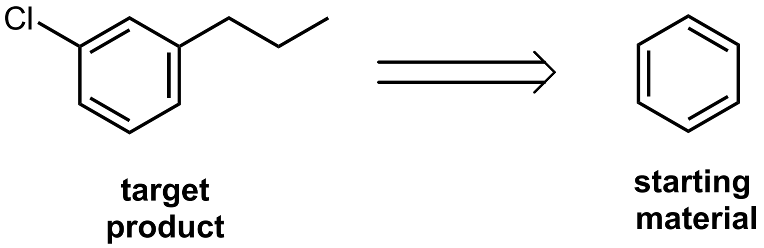
Therefore, our **full retrosynthesis** is:



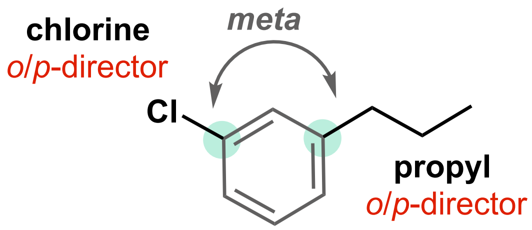
And the **forward synthesis**:



Worked Example 2



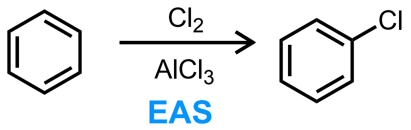
If we consider our first three questions, we see that (A) we have a **propyl group** and a **chlorine** group;. (B) the propyl group and chlorine atom are **meta** to each other; and (C) **both** the propyl group (alkyl) and the chlorine (halogen) **are *o*/*p*-directors.**



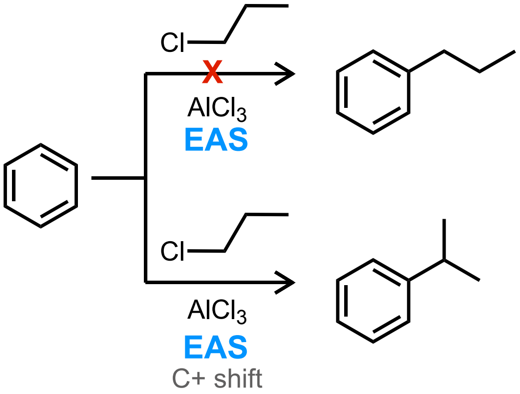
It is important to notice that neither of the two new functional groups has the correct directing effect to achieve the meta relationship we need. This suggests that we likely cannot use EAS *only*.

D. **What types of reactions** (e.g. EAS, NAS, benzylic reactions, oxidation, reduction) could introduce a propyl group and a chlorine atom in a meta relationship?

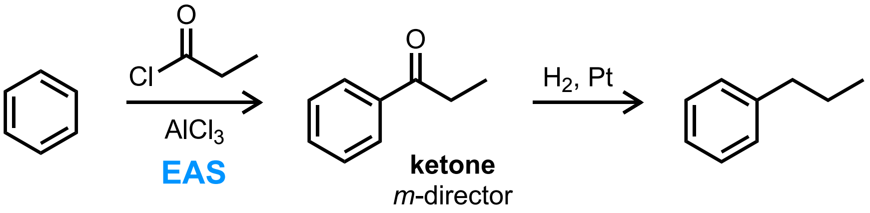
We can add the chlorine atom using EAS



But, we cannot add a propyl group through a Friedel-Crafts alkylation due to a carbocation rearrangment



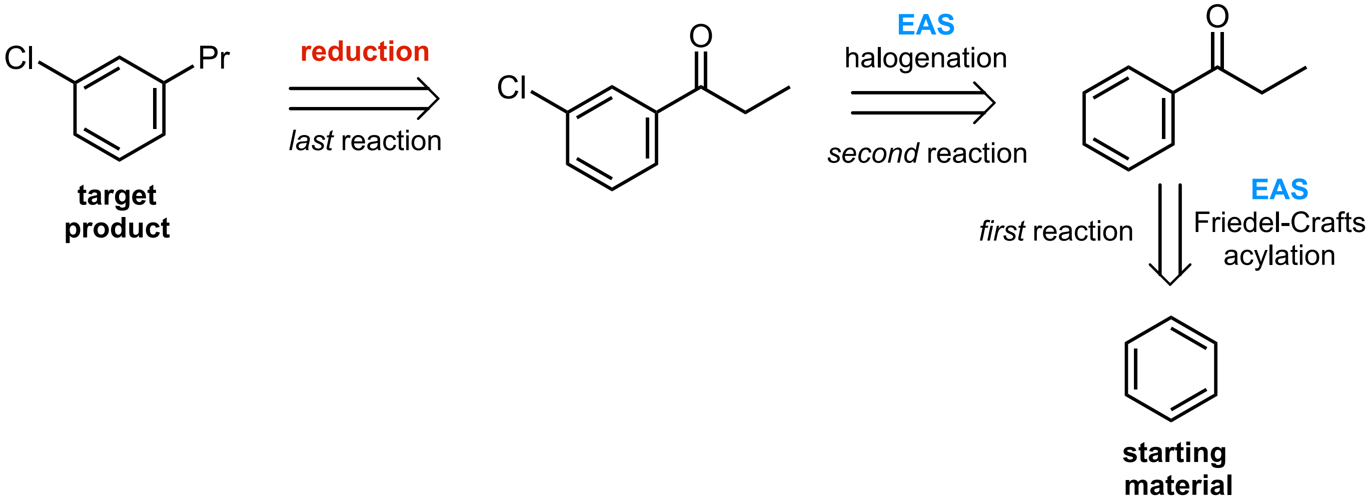
We can obtain a propyl group through the **reduction of the analogous ketone**, which we can obtain from an **EAS acylation.** Importantly, the **ketone is a *m*-director** capable of directing the chlorination to the *meta* position.



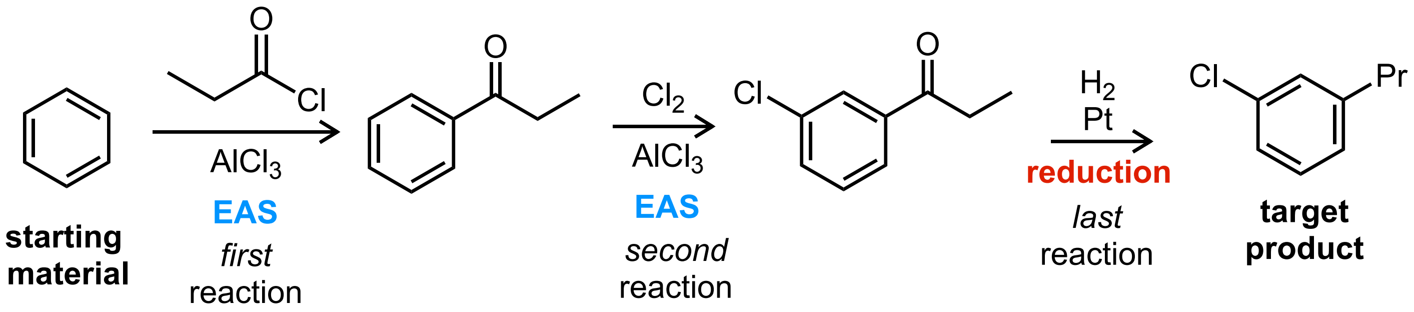
E. **What order** of these reactions is needed to achieve the para relationship?

To achieve the **meta relationship**, we must remember that the propyl group was formed through the reduction of a ketone. The ketone is itself a *m*-director. Thus, the ketone would need to be installed prior to the halogen.

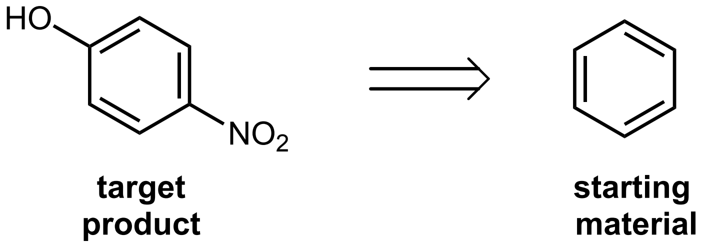
Therefore, our **full retrosynthesis** is:



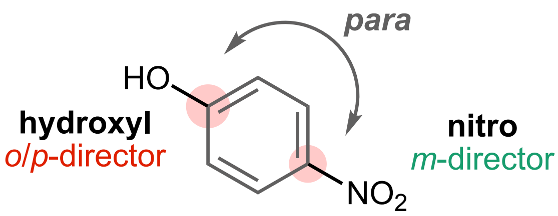
And the **forward synthesis**:



Worked Example 3

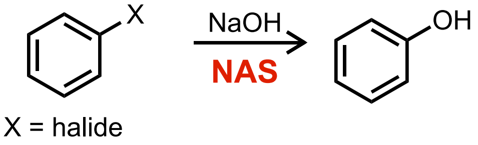


If we consider our first three questions, we see that (A) we have a **hydroxyl group** and a **nitro** group;. (B) the hydroxyl group and nitro group are **para** to each other; and (C) the **hydroxyl group is an *o*/*p*-director** whereas **the nitro group** is a ***m*-director**.

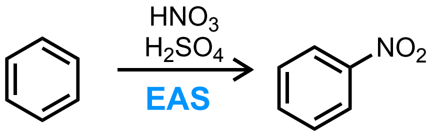


D. **What types of reactions** (e.g. EAS, NAS, benzylic reactions, oxidation, reduction) could introduce a propyl group and a chlorine atom in a meta relationship?

Alcohol can likely be introduced **through NAS**



Nitro can be added **through EAS**

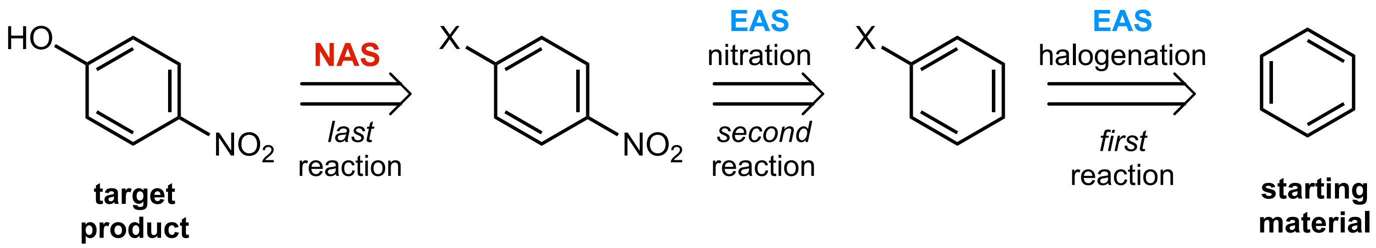


E. **What order** of these reactions is needed to achieve the para relationship?

To achieve a para relationship, we must consider that the alcohol was formed through NAS using a halide leaving group. Therefore, we need a para relationship between a halide and the nitro group. Based on this, **we need to add the halide first, which will direct the nitration reaction to the para site.**

NAS reactions benefit from an electron-poor ring, which can be provided by the electron withdrawing nitro group.

Therefore, our **full retrosynthesis** is:



And the **forward synthesis**: